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MYDRIATICS
and
BETA AMINO ACIDS

By

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THESIS

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Glenn Faber Zellhoefer

ENTITLED Mydriatics and Beta-Amino Acids

BE ACCEPTED AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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In Charge of Thesis

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Recommendation concurred in*

Committee on Final Examination*

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*Required for doctor's degree but not for master's

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MYDRIATICS.

Certain compounds of the general formula R. C.R OH CH_2 NR_2, where R represents an alkyl or aromatic group, have mydriatic properties.(1) The following compounds of this general formula were synthesized to be tested for their mydriatic properties: CH_3 C Ph OH. CH_2 N $(Et)_2$, C_2H_5. C Ph OH. CH_2 N $(Et)_2$, C_3H_7. C Ph OH. CH_2 N $(Et)_2$, C_4H_9. C Ph OH. CH_2 N $(Et)_2$ and CH_3 C Ph OH. CH_2 N HCH_3.

EXPERIMENTAL WORK.

CH_3. C Ph OH. CH_2 N $(Et)_2$.

An equimolecular amount of chloracetone, dissolved in absolute ether, was added drop by drop to cold phenyl magnesium bromide. After warming for a short while, the mixture was poured on crushed ice, the ether layer washed with water containing a few cc. of sulphuric acid, and the product distilled. Under fifteen millimeters of pressure, the Chlorhydrin boiled at 122 to 125 degrees C. A yield of 36% of the theory was obtained.

Diethyl amine was dissolved in twice its volume of alcohol and a little less than one-half the molecular amount of the chlor-hydrin added. The mixture was warmed on a water bath for two hours then most of the alcohol was distilled off and the solution made acid with dilute hydrochloric acid. After wahsing with benzene to remove the chlorhydrin, the aqueous solution was made alkaline with sodium hydroxide. The amino alcohol was extracted from the aqueous solution with ether and distilled under diminished pressure.

An analysis for nitrogen gave 6.45%. Specific gravity at 28 degrees C. is .978, index of refraction is 1.519 and the boiling point is 133 to 135 degrees C. under sixteen millimeters of pressure. The yield was 48% of the theory.

C_2H_5. C Ph OH. CH_2 N $(Et)_2$.

Chloracetophenone, dissolved in absolute ether, was added slowly to a little more than an equivolecular amount of ethyl magnesium bromide. During the addition of the chloracetophenone the temperature was kept at about 5 degrees C. but after the chloracetophenone was added the solution was warmed on a water bath for a half hour. The solution was then poured on crushed ice and the ether layer washed with water containing a few cc. of sulphuric acid. The ether was distilled off and the chlorhydrin distilled under diminished pressure.

The boiling point of the C_2H_5. C. Ph OH. CH_2 Cl was 125 to 130 degrees C. under 17 millimeters of pressure. A yield of 33% of the theory was obtained.

The chlorhydrin was treated with diethyl amine in the manner described above for CH_2 C. Ph OH. CH_2 Cl. The CH_3 C. Ph OH. $CH_2N(Et)_2$ boiled at 133 to 138 degrees C. under 15 millimeters pressure. Index of refraction was 1.502 and specific gravity, .980 at 28°C, Upon analysis 6.18% of N was found. The yield was 30% of the theory.

C_3H_7 C. Ph OH. CH_2 N $(Et)_2$.

The chlorhydrin C_3H_7 C. Ph OH. CH_2 Cl was prepared by treating chloraceto-phenone with propyl magnesium bromide in the

manner described for the preparation of the C_2H_5 C. Ph OH CH_2 Cl The boiling point of the C_3H_7 C. Ph OH. CH_2 Cl is 154 to 157 degrees C. under 20 millimeters of pressure. The yield obtained was 16% of the theory.

The amino alcohol, C_3H_7 C. Ph OH. CH_2 N $(Et)_2$, was prepared by the action of C_3H_7. C Ph OH. CH_2 Cl on diethyl amine in the same manner as described for the preparation of CH_3 C. Ph OH CH_2 N $(Et)_2$ from CH_3 C. Ph OH. CH_2 Cl.

The C_3H_7 C. Ph OH. CH_2 N $(Et)_2$ boiled at 145 to 147 degrees C. under 20 millimeters of pressure. The index of refraction is 1.510 and specific gravity .993 at 28 degrees C. The yield was 13% of the theory. An analysis for nitrogen gave 5.8%.

C_4H_9 C. Ph OH. CH_2 N $(Et)_2$.

C_4H_9 C. Ph OH. CH_2 Cl was prepared by the action of chloracetophenone on butyl magnesium bromide by the same method as described for the preparation of chlorohydrins. The C_4H_9 C. Ph OH. CH_2 Cl boiled at 135° to 143 degrees C. under 15 millimeters pressure. The yield was 51% of the theory.

The C_4H_9 C. Ph OH. CH_2 Cl was treated with diethyl amine and the C_4H_9 C. Ph OH. CH_2 N $(Et)_2$ obtained boiled at 169 to 172 degrees C. under ten millimeters of pressure. The yield was 17% of the theory. The index of refraction is 1.501 and specific gravity .960 at 28 degrees C. An analysis gave 5.3% N.

CH_3 C. OH Ph. CH_2 NH CH_3

The CH_3 C. OH Ph CH_2 Cl was prepared as described in the first section of this paper.

Fifteen grams of the chlor-hydrin was dissolved in twice its volume of alcohol and methyl amine bubbled through the solution for three hours. The process for the isolation of the amino alcohol was carried out as described in the other preparation but no trace of CH_3 C. Ph OH CH_2 NH CH_3 was found in the ether extract. In the benzene extract CH_3 C. Ph OH. CH_2OH was found, indicating that the chlorine had been hydrolyzed off during the process.

Fifteen grams of CH_3 C Ph OH. CH_2 Cl was dissolved in one-third its volume of alcohol and cooled to -12°C., while methyl amine was passed into the solution. The vessel was tightly stoppered and the solution allowed to stand at room temperature over night. As in the other cases, no trace of amino alcohol was found and the chlor-hydrin suffered hydrolysis.

Ten grams of the CH_3 C. Ph OH. CH_2 Cl was placed in a glass bomb and the bomb packed in carbon dioxide snow. Seven grams of methyl amine was distilled into the bonb, the bomb sealed and heated on the steam bath for twenty-four hours. Only a trace of the amino alcohol was formed.

BETA AMINO ACIDS.

Introduction.

At present there is no satisfactory method for the production of the beta amino acids, R C. NH_2H. CH_2 COOH. In this work effort was made to treat aceto acetic ester with ammonia to form CH_3 C:NH CH_2 $COOC_2H_5$ (2) and then reduce the beta amino crotonic acid ester to CH_3 CH NH_2 CH_2 $COOC_2H_5$ by the action of hydrogen under pressure in the presence of finely divided platinum.

Experimental Part.

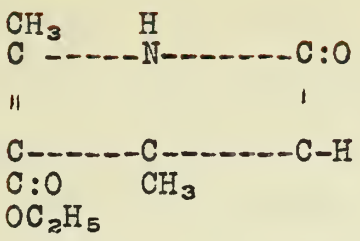
For the production of the beta amino crotonic acid ester the procedure as given by J. N. Collie (A. 226, 301) was followed. Dry ammonia gas was passed into a solution of one part aceto-acetic ester and two parts dry ether at zero degrees Centigrade. A white crystalline mass was formed, as described by Collie, which was proven to be $C_6H_{13}NO_3$. However upon standing the $C_6H_{13}NO_3$ did not split out water to form $C_6H_{11}NO_2$, as Collie described, but a disintegration into ammonia and aceto acetic ester took place, slowly at zero degrees but rapidly at room temperature. An exceptionally high grade of aceto-acetic ester (B.P. 85° -94° C. under 20 millimeters pressure) was used and the ammonia was dried by passing through lime towers of sodium hydroxide, two chilled with ice and the third chilled with carbon dioxide snow. Every precaution was made to have the reacting mixture dry and to protect it from moisture during the reaction. But even with these precautions the procedure was unsuccessful. However the splitting out of HOH from $C_6H_{13}NO_3$ to form $C_6H_{11}NO_2$ was effected by keeping a pressure of twenty pounds of ammonia

over the $C_6H_{13}NO_3$ for thirty-six hours. The mixture was kept at zero degrees centigrade. When this method was used a yield of ninety-three per cent. of the theory was obtained even though a mediocre grade of acetoacetic ester was used and no effort made to dry the ammonia. Upon standing three months some of the beta amino crotonic acid ester decomposed into acetic acid and ammonia.

To effect the reduction of the ethylic beta amido crotonate to form beta amino butyric acid ester the unsaturated product was dissolved in twice its volume of alcohol and .5 grams of platinum oxide (prepared according to the method of Voorhees and Adams, Journal of the American Chemical Society, June 1922, page 1397) added. The mixture was agitated for forty-eight hours under a pressure of forty pounds of hydrogen. This method proved unsuccessful so the solution was acidified with acetic acid. This likewise failed to effect reduction.

The hydrochloride of the beta amino crotonic acid exter was prepared by passing perfectly dry hydrochloride into a solution of 25 grams of the crotonate and 25 grams of dry ether, (Soc. 71, 303). The ether was then decanted off and absolute alcohol added with .5 grams of the platinum oxide. The mixture was agitated under about forty pounds pressure of hydrogen for twenty hours. About .2 moles of H_2 reacted. The product was filtered and in the precipitate was ammonium chloride and a compound which proved to be $C_6H_{13}NO_2$

This compound has been isolated by Collie (Soc. 71, 303) and identified by F. N. Fleischman (Soc. 91, 257) as



The product was purified by recrystalization from hot water. The melting point was 138-139°Centigrade. Analysis for the nitrogen gave the following results:

Sample.	.3000 grams	.3000 grams.
Nitrogen	.02156 "	.02128 "
Per Cent of N	7.12%	7.09%
Theory	7.2 %	7.2%

After distilling off the alcohol in the filtrate a resinous product remained which was water insoluble and ether soluble. It suffered decomposition at about 150° when effort was made to distill it under 20 millimeters of pressure.

Evidently some products of disintegration of the crotonate hydrochloride formed a platinum salt, (Soc. 71, 303-311) for the theoretical amount of platinum black was not recovered and the resinous material derived from the filtrate contained platinum as indicated by tests made on its residues after ignition.

In hope that the benzal amino crotonic acid ester could be reduced without suffering rearrangement it was prepared (B. 26, 467) by treating equimolecular amounts of benzaldehyde and beta amino crotonic acid ester and heating on the steam bath for fifteen minutes. The benzal amino crotonic acid ester is a viscuous product which suffers decomposition when attempt is made to distill it under fifteen millimeters of pressure. No

effort was made to effect its reduction.

Summary and Conclusion.

While it is possible to obtain the beta amino crotonic acid ester in excellent yields by the action of ammonia upon aceto acetic ester it is not possible to effect the reduction by the action of hydrogen under pressure with platinum as a catalyst because of rearrangement of the molecule. However it is possible that a derivative of the beta amido crotonate, or some homologue can be satisfactorily reduced by this method.

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